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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/076,934	02/15/2002	Richard M. O'Hara JR.	WYS-00701	3689

58571 7590 07/25/2006

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EXAMINER	
OUSPENSKI, ILIA I	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 07/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/076,934	O'HARA ET AL.	
	Examiner	Art Unit	
	ILIA OUSPENSKI	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,9-12 and 28-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,9-12 and 28-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/15/2006 has been entered.

2. Applicant's amendment/remarks, filed 03/15/2006, are acknowledged.

Claims 6 – 8, 14 – 20, and 22 – 27 have been cancelled.
Claims 5, 13, and 21 have been cancelled previously.
Claims 1 and 9 have been amended.
Claims 28 – 31 have been added.

Claims 1 – 4, 9 – 12, and 28 – 31 are pending.

3. This Office Action will be in response to applicant's amendment and arguments, filed 03/15/2006.

The rejections of record can be found in the previous Office Action, mailed 09/14/2005.

The text of those sections of Title 35 USC not included in this Action can be found in a prior Office Action.

It is noted that New Grounds of Rejection are set forth herein.

4. The objection of record has been withdrawn in view of Applicant's amendment and arguments.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1 – 4, 9 – 12, and 28 – 31 are rejected under **35 U.S.C. 112, first paragraph**, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a New Matter rejection.*

Applicant's amendment does not point out where the support for the newly added limitations comes from, and the specification as-filed or original claims do not appear to provide adequate written description of the following limitations:

A. "treating type I diabetes." The disclosure appears to provide support for a method of therapeutically downmodulating an autoimmune response in a subject having type I diabetes (e.g. pages 3 – 4), which is not seen as providing sufficient support under 35 USC 112, first paragraph, for the above recitation.

B. "inhibiting the onset of type I diabetes in a subject." The specification discloses e.g. at page 48 that PV1-scFv prevents disease onset in NOD mice; this disclosure does not provide sufficient support for the above generic recitation.

The instant claims now recite limitations which were not clearly disclosed in the specification and claims as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in the present claims, which did not appear in the specification or original claims, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the New Matter in the response to this Office Action. Alternatively, Applicant is invited to clearly point out the written support for the instant limitations.

7. Claims 1 – 4, 9 – 12, and 28 – 31 are rejected under **35 U.S.C. 112, first paragraph**, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention.

The specification does not enable one of skill in the art to treat type I diabetes or to inhibit the onset of type I diabetes by administering an antigen-binding portion of a blocking anti-CD28 antibody, as claimed, without undue experimentation. Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, limited working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

Applicant ahs disclosed that PV1 scFv inhibits T cell responses in vitro and delays onset of diabetic symptoms in NOD mice (e.g. Examples 2 – 4 at pages 48 – 49).

This is not seen as sufficient enabling description of the claimed methods, for the following reasons.

Animal models of type I diabetes have not correlated well with in vivo clinical trial results in patients. For example Aly et al. (Am. J. Therap., 2005, 12: 481 – 490; see entire document) review, in particular with regard to the NOD mice model, that humans are likely to have a less reversible progression of type I diabetes that animal models, and may require more robust treatment than model animals (e.g. page 483 first column). Since the efficacy of therapeutic antibodies can be species- and model-dependent, it is not clear that reliance on the experimental observations in the experimental model described in the instant specification provide the basis for employing antigen-binding portion of a blocking anti-CD28 antibody for treating type I diabetes. For example, Blazar et al. (J. Immunol., 1996, 157: 3250 – 3259; see entire document, in particular, e.g. page 3257, column 2 first paragraph) disclose that issues such as tissue distribution, half-life, affinity and avidity obtained with various antibodies targeting costimulatory molecules might prove to be highly important in achieving a therapeutic effect. However, any conclusion regarding the efficacy of CD28/B7 modulation on altering in vivo immune response should be interpreted in light of the specific reagent used (Blazar et al., see page 3257, column 2, paragraph 1). Therefore, there is no evidence that the animal model used in the experiments disclosed in the specification would be predictive of the therapeutic methods encompassed by the claims.

Furthermore, it is estimated that in type I diabetes, over 80% of the tissue targeted by the autoimmune response is destroyed before the disease becomes clinically manifest (e.g., Bach J., Immunology Today, 1993, 14: 322 – 326; see entire

document, in particular, e.g. paragraph bridging pages 324 – 325). Consequently, the skilled artisan would not find it predictable that an on-going autoimmune disease could be treated when the guidance provided in the specification is limited to preventing initiation of an induced disease.

With regard to the recitation of "inhibiting the onset of type I diabetes," it is noted that the recitation is interpreted as equivalent to "preventing," i.e. encompassing a complete inhibition of the onset of the disease. The burden of enabling the prevention of a disease would be greater than that of enabling a treatment due to the need to screen those humans susceptible to such diseases and the difficulty of proof that the administration of the drug was the agent that acted to prevent the condition. Further, the specification does not provide guidance as to how one skilled in the art would go about screening those patients susceptible to type I diabetes within the scope of the presently claimed invention. Nor is guidance provided as to a specific protocol to be utilized in order to prove the efficacy of the presently claimed compounds in preventing these disease states. Accordingly, undue experimentation is necessary to develop the screening and testing protocols in order to enable the practice of the presently claimed methods.

In view of insufficient guidance by the instant specification and the lack of predictability of the art to which the invention pertains with respect to the CD28 signaling pathway, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of the clinical protocols, and absent working examples providing evidence that the claimed methods are effective for treating type I diabetes or inhibiting the onset of type I diabetes by administering an antigen-binding portion of a blocking anti-CD28 antibody.

8. Claims 29 and 31 are rejected under **35 U.S.C. 112, first paragraph**, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention.

It is apparent that the PV1 antibody is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the cell line or hybridoma which produces this antibody. See 37 CFR 1.801-1.809.

If the deposit has been made under the terms of the Budapest Treaty, an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the hybridoma has been deposited under the Budapest Treaty would satisfy the deposit requirement made herein.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

9. Claims 1 – 2 and 9 – 10 stand rejected under **35 U.S.C. 102(b)** as being anticipated by Linsley et al. (US Pat. 5,521,288, see entire document) as evidenced by Paul (Fundamental Immunology, 1999, page 451).

Applicant's arguments have been fully considered but have not been found convincing.

Applicant argues that Linsley et al. do not enable methods of treating type I diabetes.

This is not found persuasive, because Linsley et al. teach blocking anti-CD28 antibodies can be used to treat insulin-dependent diabetes mellitus (column 36 lines 36 – 43). It is accepted in the art that insulin-dependent diabetes mellitus is a synonym of type I diabetes.

Therefore, the rejection of record is maintained for the reasons of record, as it applies to the amended claims. The rejection or record is incorporated by reference herein, as if reiterated in full.

10. Claims 1 – 4 and 9 – 12 stand rejected, and newly added claims 28 and 30 are rejected, under **35 U.S.C. 102(e)** as being anticipated by Yu et al. (US Pat. Pub. 2002/0006403, see entire document) as evidenced by Paul (Fundamental Immunology, 1999, page 451).

Applicant's arguments have been fully considered but have not been found convincing.

Applicant argues that Yu et al. do not enable methods of treating type I diabetes.

This is not found persuasive, because Yu et al. teach that blocking anti-CD28 antibodies can be used to treat autoimmune diseases, such as diabetes mellitus (see Summary of Invention at paragraphs 0010 – 0023, and in particular paragraph 0013). It is accepted in the art that autoimmune diabetes mellitus is a synonym of type I diabetes.

Therefore, the rejection of record is maintained for the reasons of record, as it applies to the amended claims. The rejection or record is incorporated by reference herein, as if reiterated in full.

11. Conclusion: no claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILIA OUSPENSKI whose telephone number is 571-272-2920. The examiner can normally be reached on Monday-Friday 9 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Art Unit 1644
July 18, 2006

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7/18/06